Associations between serum albumin and serious non-AIDS events among people living with HIV

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Abstract: OBJECTIVE Lower serum albumin (sAlb) has been associated with an increased risk of mortality and AIDS among people living with HIV and may be associated with the development of serious non-AIDS events (SNAEs). We evaluated the long-term association between sAlb and the risk of SNAEs. DESIGN Prospective multinational cohort study. METHODS D:A:D participants without SNAEs were followed from first routine sAlb value to the first of a new SNAE [cardiovascular disease (CVD), end-stage liver disease (ESLD), end-stage renal disease (ESRD), non-AIDS malignancy (NADM), death from non-AIDS cause], AIDS-death, 6 months after last visit or 01/02/2016. Poisson regression was used to determine associations between sAlb and a new i) SNAE, ii) CVD or iii) NADM event, with adjustment for potential confounders. Models additionally tested whether the associations were modified by age, follow-up time, smoking status, CD4 and viral load. RESULTS Of 16,350 participants (71.8% male, median age 44 years) 1,463 developed a SNAE (371 CVD, 200 ESLD, 40 ESRD, 553 NADM, 299 deaths from other non-AIDS causes) over 80,264 person-years. Increased sAlb was associated with a decreased risk of an SNAE (adjusted rate ratio (aRR) per 5 g/L: SNAE 0.79 [95%CI: 0.76, 0.83]; CVD 0.87 [0.80, 0.94]; NADM 0.88 [0.82, 0.95]). The association did not appear to wane with additional years of follow-up (p-interaction = 0.79) but was stronger for current smokers than for never smokers (p-interaction<0.01). CONCLUSIONS sAlb is a durable risk factor for SNAE. Future studies are needed to determine the mechanism underlying this association and to evaluate the value of sAlb in predictive tools.

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Associations between serum albumin and serious non-AIDS events among people living with HIV

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Abstract

Objective: Lower serum albumin (sAlb) has been associated with an increased risk of mortality and AIDS among people living with HIV and may be associated with the development of serious non-AIDS events (SNAEs). We evaluated the long-term association between sAlb and the risk of SNAEs.

Design: Prospective multinational cohort study.

Methods: D:A:D participants without SNAEs were followed from first routine sAlb value to the first of a new SNAE [cardiovascular disease (CVD), end-stage liver disease (ESLD), end-stage renal disease (ESRD), non-AIDS malignancy (NADM), death from non-AIDS cause], AIDS-death, 6 months after last visit or 01/02/2016. Poisson regression was used to determine associations between sAlb and a new i) SNAE, ii) CVD or iii) NADM event, with adjustment for potential confounders. Models additionally tested whether the associations were modified by age, follow-up time, smoking status, CD4 and viral load.

Results: Of 16,350 participants (71.8% male, median age 44 years) 1,463 developed a SNAE (371 CVD, 200 ESLD, 40 ESRD, 553 NADM, 299 deaths from other non-AIDS causes) over 80,264 person-years. Increased sAlb was associated with a decreased risk of an SNAE (adjusted rate ratio (aRR) per 5g/L: SNAE 0.79 [95%CI: 0.76, 0.83]; CVD 0.87 [0.80, 0.94]; NADM 0.88 [0.82, 0.95]). The association did not appear to wane with additional years of follow-up (p-interaction=0.79) but was stronger for current smokers than for never smokers (p-interaction<0.01).

Conclusions: sAlb is a durable risk factor for SNAE. Future studies are needed to determine the mechanism underlying this association and to evaluate the value of sAlb in predictive tools.

Keywords: albumin, biomarker, cancer, CVD, non-AIDS comorbidity, smoking

INTRODUCTION

Exploring novel associations between biomarkers and serious non-AIDS events (SNAE) may inform disease pathogenesis. Low serum albumin (sAlb) has consistently been associated with AIDS progression and all-cause mortality in people living with HIV (PLWH) [1-6]. Moreover, the association of sAlb with SNAE was recently assessed in the INSIGHT START Study [7]. SAlb was independently associated with SNAE over the short-term and, potentially, over the longer term. Due to a limited sample size and duration of follow-up, this study was not powered to detect associations with specific SNAE, assess important effect modifiers, or to determine the duration over which the association remained present.

Using data from the Data on Adverse Events of Antiretroviral Drugs (D:A:D) Study we aimed to undertake a detailed evaluation of the association between sAlb and SNAE in a larger and more heterogeneous study population with longer follow-up.

METHODS

Study design

The D:A:D Study is an observational study following approximately 50,000 PLWH from 11 cohorts in Europe, USA and Australia. Collected data include information on socio-demographic factors, HIV-related factors including AIDS events and antiretroviral treatment (ART) regimens, and other non-AIDS risk factors.

A SNAE was systematically collected (https://www.chip.dk/Studies/DAD/Study-Documents) and defined as CVD (myocardial infarction, stroke, invasive cardiovascular procedure or death from CVD); end-stage renal disease (ESRD) or death from renal disease; end-stage liver disease

(ESLD) or death from ESLD; non-AIDS-defining malignancies (NADMs, except for basal cell or squamous cell skin cancer) or death from cancer; and any other non-AIDS death.

We excluded cohorts that did not provide any or sparse sAlb data (online supplement M1, http://links.lww.com/QAD/B297). We selected a baseline date for each cohort which reflected the time at which the coverage of sAlb measurements increased to a level that suggested routine monitoring. As the systematic collection of some SNAE did not commence until 1st February 2004, each cohort-specific baseline date was set to the later of this date or the date of routine sAlb monitoring. The date of the closest sAlb measurement to this cohort-specific date (as long as the sAlb had been measured less than one year prior to this date) was taken to be the individual baseline date. Individuals without a sAlb measurement in this window were excluded, as were those who already had a SNAE at their baseline.

Statistical methods

Study participants were followed from baseline to the date of each endpoint; follow-up for each person was censored on the date of an AIDS death, six months after the last clinic visit or on 1st February 2016, whichever occurred earliest. Follow-up times for analyses of the CVD and NADM endpoints were additionally censored on the date of a non-CVD/non-NADM SNAE.

Poisson regression was used to model the rate of the three endpoints; unadjusted and adjusted rate ratios (RR/aRR) and 95% confidence intervals (CIs) were computed. We considered a fixed model with covariates defined on the baseline date.

Selection of confounders for inclusion in multivariable models was based on available information about the relation between sAlb and SNAE. Covariates that were included were participating cohort, gender, risk group, race, age, body-mass index (BMI), smoking status

(current smoker, ex-smoker, never smoker, unknown), dyslipidaemia (total cholesterol (TC) ≥6.2 mmol/l, high-density lipoprotein cholesterol (HDL-C) ≤0.9 mmol/l, TC:HDL-C ratio ≥6.5 or receipt of lipid lowering drug), ALT and estimated glomerular filtration rate (eGFR)(Cockcroft-Gault equation), hepatitis C-virus (HCV)(positivity by anti-HCV and/or HCV RNA positive), hepatitis B-virus (HBV)(positivity by HBsAg, HBeAg or HBV-DNA positive/anti-HBe positive), CD4 count, viral load (VL)<50 copies/ml, current exposure to each antiretroviral class. All variables were continuous unless specified otherwise.

We also assessed interactions between i) sAlb and age; ii) sAlb and cigarette smoking; iii) sAlb and follow-up time; iv) sAlb and baseline CD4 count; and v) sAlb and the latest HIV RNA (as a time-updated covariate). Analyses were conducted in SAS version 9.3.

RESULTS

Of the 33,750 potentially eligible individuals, 16,350 had a baseline sAlb measurement and were free of SNAE at this time. The characteristics of the individuals excluded at this stage did not differ substantially from those of the included participants (male 74.1% vs. 71.8%; heterosexual 35.5% vs. 36.4%; white ethnicity 50.0% vs. 50.5%; median age 38 vs. 37 years; previous exposure to ART 62.4% vs. 63.3%, median CD4 cell count 408 vs. 420 cells/mm^3). A detailed description of study participants is provided in online supplement M2, http://links.lww.com/QAD/B297.

Study participants were followed for a total of 80,264 person-years (PYRS), during which 1463 SNAE were observed. This included 371 (25.4%) CVD events, 553 (37.8%) NADM events, 200 (13.7%) ESLD events, 40 (2.7%) ESRD events and 299 (20.4%) deaths from other SNAE.

PYRS, event rates, and number of events stratified by sAlb levels are depicted in online supplement M3, http://links.lww.com/QAD/B297.

Lower sAlb was associated with all events considered and RRs were only modified slightly after adjustment (Table 1). Moreover, various strata of lower levels of sAlb appeared to be associated with higher SNAE rates suggesting a linear association. Whilst associations were numerically weaker for the CVD and NADM endpoints, the trend for a higher event rate in those with lower sAlb levels was still apparent (online supplementary M2, http://links.lww.com/QAD/B297).

We tested several interactions (Figure 1). The association between sAlb and SNAE was slightly stronger in younger individuals (p-interaction<0.001). For SNAE the association with sAlb seemed to differ by baseline CD4+ cell count with the strongest effect seen among individuals with CD4+ cell counts below 200 cells/mm^3 (p-interaction<0.001). The association between sAlb and SNAE was still evident six years after baseline sAlb measurement in the fully adjusted model and there was no evidence that the association between sAlb and SNAE changed over time (p-interaction=0.79). We found evidence for an interaction between smoking and sAlb with a stronger association for current smokers compared to never smokers (aRR 0.76 [95%CI: 0.73-0.80] vs aRR 0.87 [95%CI: 0.80-0.95], p<0.01). Finally, analyses revealed some effect modification with the latest viral load for the SNAE, with associations being slightly stronger in those with a non-suppressed viral load (p-interaction<0.001).

DISCUSSION

We found a strong association between lower sAlb and SNAE. This observation was consistent across different SNAE and did not appear to wane over time since sAlb measurement. The

association between sAlb and SNAE appeared to be stronger in younger individuals and in current smokers.

Several studies have found an association between sAlb and all-cause mortality in PLWH. One of the earliest studies from the Women's Interagency HIV Study suggested that sAlb could be associated with non-AIDS causes of mortality, as sAlb was found to be a more strongly associated with mortality in individuals with high CD4 counts [3]. A US veterans study confirmed this and noted a strong independent association between sAlb and atherosclerotic CVD events and heart failure [5]. SAlb was also recently shown to be associated with SNAE in the START study. Our study confirmed these findings and demonstrated that sAlb was associated with both CVD and NADM.

Several factors may confound our observations. Although low sAlb is commonly regarded as a marker of nutritional status, it is poorly associated with other measures of nutritional status in the general population and in PLWH [8, 9]. Other causes of low sAlb may include liver disease (decreased synthesis), enhanced turnover resulting from either increased catabolism or enhanced loss of albumin into the urine or intestine [10], or trans-capillary loss due to increased vascular permeability [11]. The acute phase response, of which interleukin (IL)-6 is a potent inducer, to infectious conditions, neoplastic growth, or immunological disorders, is also associated with inhibition of liver protein synthesis in animal studies [12]. A lowering of sAlb may therefore reflect the chronic inflammation that has been associated with HIV infection [13]. In the START study, however, sAlb was associated with SNAE even after adjusting for IL-6 levels [7]. A low sAlb level might be a consequence of other pathways of immune activation that may be less directly associated with the inflammatory marker IL-6. Moreover, the neonatal Fc receptor, expressed in many different cell types and induced by pro-inflammatory cytokines like TNF-α

and IL-1β [14], protects sAlb from degradation [15]. Finally, sAlb may exert a protective effect due to antioxidant activity, binding capacity of endogenous and exogenous compounds (e.g. fatty acids and carcinogens) [16], or its anti-thrombotic effects [17].

We also showed that sAlb was associated with disease endpoints even when the level was measured six years before the occurrence of a SNAE and when sAlb was within the range of levels commonly considered as normal (>35 g/L). Individuals with sAlb levels of 35-40 g/L (low-normal), controlling for other factors, were more likely to experience a SNAE than individuals with levels of 40-45 g/L (high-normal). SAlb even seemed to exert a protective effect at high levels (>45 g/L). Thus, the association with SNAE appeared to be linear with no obvious threshold effect.

A few interventions may cause changes to sAlb levels. Initiation of cART was associated with higher sAlb concentration during follow-up when compared to participants who deferred cART initiation [7]. Smoking cessation has been associated with increases in sAlb with levels changing towards those of never smokers within five years [18]. We showed that the association between sAlb and SNAE was strongest in current smokers, in line with earlier studies from the general population [18, 19]. Mechanisms underlying the potential effects of interventions on sAlb levels or in which ways factors modify the association between sAlb and SNAE are unknown. As the correlation between cumulative smoking and sAlb was weak, it was previously suggested that those smokers with lowest sAlb levels were those with the greatest inflammatory response to smoking [18]. Consistent with this, newer evidence shows that smoking is associated with extensive alterations in systemic markers of inflammation of which many revert back to levels of never smokers after smoking cessation [20]. sAlb levels may consequently be a proxy for susceptibility to the effect of noxious stimuli, such as smoking, but potentially also to

inflammation associated with HIV. Accordingly, we also observed an association between sAlb and SNAE in those who reported never smoking in contrast to studies from the general population [18, 19], and we showed that viral suppression modified the association between sAlb and SNAE, which indicate that the association is not driven completely independent of HIV.

Our study has limitations. First, SAlb concentrations were measured irregularly in the contributing cohorts. To avoid the confounding effect of increased monitoring in sick individuals, we considered a fixed timepoint analysis. Secondly, not all eligible individuals had a sAlb measurement, which may have introduced selection bias, although we observed characteristics of individuals with and without sAlb measurements to be similar.

In conclusion, sAlb was found to be independently associated with SNAE, including CVD and NADM. This association did not appear to wane over time and was strongest in current smokers. The pathophysiology underlying the relationship between sAlb and SNAE, and its effect modifiers, are poorly understood, and warrants further mechanistic investigation.

Contributions

AR, CIH, LR, JDL, AP, and CS developed the initial analysis protocol. CIH and LR performed study coordination and prepared the datasets for analysis. CS performed the statistical analyses. AR prepared the first draft of the manuscript and completed all revisions. All authors provided critical input at all stages of the preparation of the manuscript.

Declaration of interests

AR, CIH, LR, FB, WES, RW, SdW, JDL, and ANP have no disclosures to declare. PR has through his institution received independent scientific grant support from Gilead Sciences,

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Participating physicians: P. Dellamonica, E. Bernard, J. Courjon, E. Cua, F. De Salvador-Guillouet, J.Durant, C. Etienne, S. Ferrando, V. Mondain-Miton, A. Naqvi, I. Perbost,S. Pillet , B. Prouvost-Keller, P. Pugliese, V. Rio, K. Risso, P.M. Roger.

SHCS (Swiss HIV Cohort Study, Switzerland):

The data are gathered by the Five Swiss University Hospitals, two Cantonal Hospitals,15 affiliated hospitals and 36 private physicians (listed in http://www.shcs.ch/180-health-care-providers).

Members of the Swiss HIV Cohort Study:

Aubert V, Battegay M, Bernasconi E, Böni J, Braun DL, Bucher HC, Calmy A, Cavassini M, Ciuffi A, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Günthard HF (President of the SHCS), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kouyos RD, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Marzolini C, Metzner KJ, Müller N, Nicca D, Pantaleo G, Paioni P, Rauch A (Chairman of the Scientific Board), Rudin C (Chairman of the Mother & Child Substudy), Scherrer AU (Head of Data Centre), Schmid P, Speck R, Stöckle M, Tarr P, Trkola A, Vernazza P, Wandeler G, Weber R*, Yerly S.

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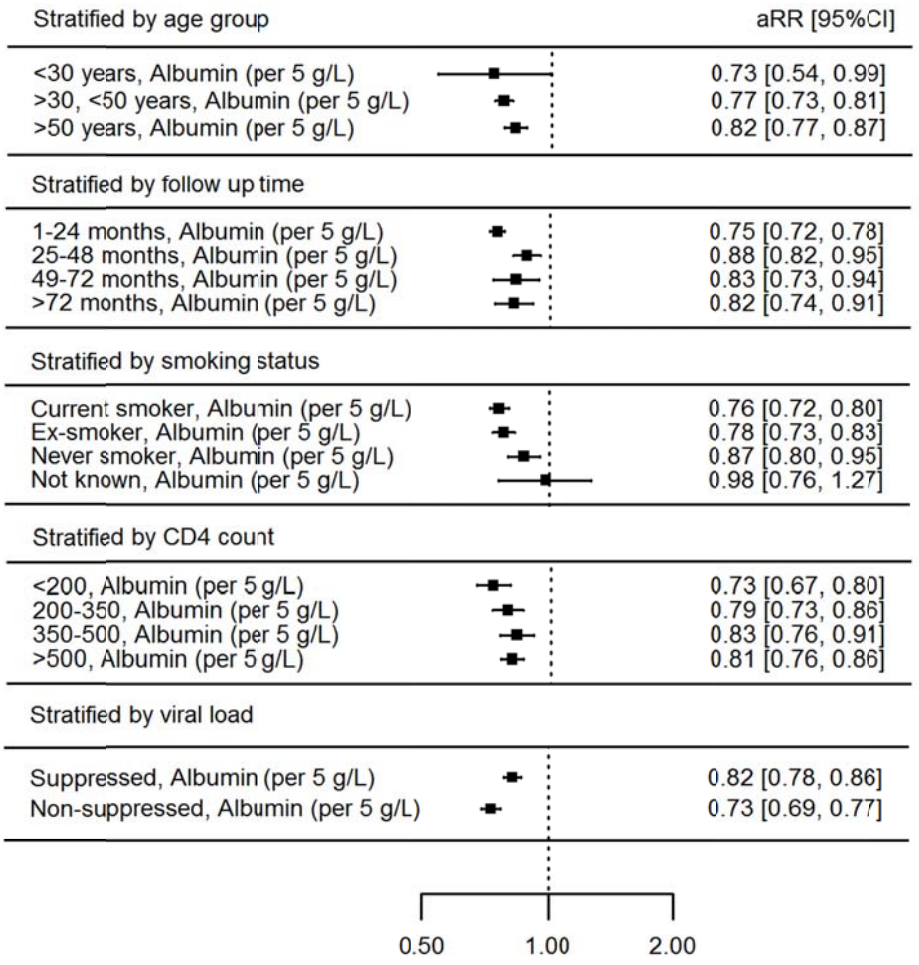
Table 1: Unadjusted and adjusted association between baseline sAlb value and a) any SNAE, b) any CVD event, and c) any NADM, obtained from Poisson regression analysis.

		Unadjusted		Adjusted	
		RR (95% CI)	p-value	aRR (95% CI)	P-value
a) Any SNAE					
Albumin (g/L)	<30	4.57 (3.74, 5.58)	<0.0001	3.57 (2.89, 4.40)	<0.0001
	≥30, <35	2.52 (2.07, 3.07)	<0.0001	2.30 (1.88, 2.82)	<0.0001
	≥35, <40	1.50 (1.31, 1.71)	<0.0001	1.33 (1.16, 1.52)	<0.0001
	≥40, <45	Ref.	-	Ref.	-
	≥45, <50	0.77 (0.67, 0.89)	<0.001	0.82 (0.71, 0.95)	<0.01
	≥50	0.63 (0.45, 0.89)	<0.01	0.73 (0.51, 1.03)	0.07
Albumin (continuous, per 5g/L)		0.75 (0.73, 0.78)	<0.0001	0.79 (0.76, 0.82)	<0.0001
b) Any CVD event					
Albumin (g/L)	<30	1.12 (0.55, 2.29)	0.75	1.23 (0.60, 2.51)	0.58
	≥30, <35	1.79 (1.16, 2.74)	<0.01	2.33 (1.50, 3.62)	<0.001
	≥35, <40	1.34 (1.03, 1.75)	0.03	1.31 (1.00, 1.71)	0.05
	≥40, <45	Ref.	-	Ref.	-
	≥45, <50	0.83 (0.64, 1.07)	0.15	0.81 (0.62, 1.07)	0.13
	≥50	0.60 (0.30, 1.17)	0.13	0.63 (0.32, 1.24)	0.18
Albumin (continuous, per 5g/L)		0.87 (0.80, 0.94)	<0.001	0.87 (0.80, 0.94)	<0.001
c) Any NADM event					
Albumin (g/L)	<30	2.44 (1.63, 3.66)	<0.0001	1.98 (1.28, 3.04)	<0.01
	≥30, <35	1.64 (1.14, 2.36)	<0.01	1.54 (1.05, 2.24)	0.03
	≥35, <40	1.12 (0.89, 1.41)	0.32	1.00 (0.79, 1.26)	0.98
	≥40, <45	Ref.	-	Ref.	-

≥45, <50	0.84 (0.68, 1.04)	0.11	0.92 (0.74, 1.14)	0.44
≥50	0.80 (0.49, 1.29)	0.35	0.94 (0.58, 1.53)	0.81
Albumin (continuous, per 5g/L)	0.84 (0.79, 0.89)	<0.0001	0.88 (0.82, 0.95)	<0.001

[1]Adjusted for participating cohort, gender, risk group, race, and the following covariates defined at baseline: age, BMI, smoking status, dyslipidaemia, total cholesterol, ALT, eGFR, HCV, HBV, CD4, VL≤50 copies/ml, current exposure to NRTIs, PIs, NNRTIs and INSTIs. Abbreviations: CVD, cardiovascular disease; NADM, non-AIDS defining malignancy; RR, rate ratio; SNAE, serious non-AIDS event.

Figure 1. Interactions of serum albumin with age group, follow up time, smoking status, CD4 count and viral load levels.



P-value for interactions was <0.0001 for age, <0.001 for CD4 count, and 0.79 for follow-up time. The association for current smokers was different than for never-smokers (p-value<0.01, see results) and different for virally suppressed individuals vs. non-suppressed (p-value<0.001). Abbreviations: aRR, adjusted rate ratio.